Environmental Health Perspectives
Vol. 72, p. 201, 1987

Introduction

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The scientific community recently began to expand its development of *in vitro* test methods as alternatives or adjuncts to standard toxicologic studies. Although these tests could not completely replace whole animal testing, the tiered approach that they provided did reduce the number of chemicals that had to be tested with live animals. *In vitro* tests appear to offer several advantages over standard whole animal toxicologic approaches: they use either no mammals or a smaller number of mammals than the standard studies, and they frequently can be completed more rapidly and with fewer resources than standard *in vivo* methods. Under certain circumstances, *in vitro* techniques also allow control over the dose that reaches the site of toxicologic action, permit more rapid determination of the proximate toxicant, and facilitate determinations of the mechanism(s) of action.

One area of toxicology that has been developing rapidly in recent years is that which seeks alternatives to whole animal teratology testing. A number of systems are currently being developed as screens for teratogens. Therefore, the Division of Toxicology in the Food and Drug Administration's (FDA) Center for Food Safety and Applied Nutrition convened an internal task force to compile and review information on test systems currently under development as adjuncts to classical whole animal teratology testing procedures. The members were chosen from staff scientists who represent a broad range of scientific backgrounds and expertise.

The task force members began by reviewing the report of a consensus workshop (*1*) that evaluated several *in vitro* test systems as potential screens for teratogens. This consensus workshop was sponsored by the FDA, the Interagency Regulatory Liaison Group, and the Environmental Protection Agency. The task force agreed to adopt the consensus workshop's definition of *in vitro* (i.e., "any system that employs test subjects other than the intact pregnant mammal") and to initiate literatures searches to complement and expand the work that had been completed by the consensus workshop.

On-line literature searches were conducted to obtain pertinent articles published through spring 1986. Papers published after spring 1986 and foreign language articles that could not be obtained and translated in a timely manner were not reviewed. Papers that were found to describe cytotoxicity assays, developmental biology procedures, and other test systems that were not specifically designated as teratology testing procedures by their developers were excluded from further consideration. More than 600 relevant journal articles were identified, and these were divided into five subcategories for critical evaluation, as follows: mammalian whole embryo culture, rodent limb bud culture, embryonic organs in culture, cells in culture, and nonmammalian model systems.

Factors that were evaluated for each *in vitro* test system included the end point(s) measured (e.g., biochemical, morphological, or radiochemical); the diversity of compounds testable in the system based on physical state or solubility; the presence of an endogenous metabolic activation system or the feasibility of using an exogenous activation system; the degree of system standardization; the ability to correlate the *in vitro* results with any known *in vivo* findings; the test's utility for providing information on possible mechanisms of action; and practical aspects such as the general complexity of the techniques and equipment used to conduct tests and the length of time required to complete a test. In addition to a critical review of the published literature, task force members obtained supplemental information through personal communications with the authors and other researchers. Such information included the type of expertise required to conduct the *in vitro* test, the resources (i.e., personnel and costs) required to implement and use the systems, and the ongoing validation efforts.

The task force members prepared written reviews that were used to assess the status of *in vitro* teratology testing as of spring 1986. The following reviews are the reports of the task force. Any opinions stated or implied in these articles are solely those of the task force members. They are not meant to reflect any current or future regulatory policies of the FDA.

We would like to acknowledge June Bradlaw, Benjamin Jackson, David Hattan, and Carol Mapes for their review and commentary, and Helen Reynolds, Norma Yess, and Lois Tomlinson for editorial assistance.

REFERENCE

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